

Microwave Chemistry: General Features and Applications

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ABSTRACT

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As we know fire is now rarely used in synthetic chemistry, it was not until Robert Bunsen invented burner in 1855 that the energy from this heat source could be applied to a reaction vessel in a focused manner. The Bunsen burner was later superseded by the heating mantle, oil bath or hot plate as a source of heat to a chemical reaction. In the past few years, heating chemical reactions by microwave energy has been an increasingly popular theme in the scientific community. The use of microwave irradiation in chemistry has become a popular technique that it might be assumed that, in a few years, most chemists will probably use microwave energy to heat chemical reactions on a laboratory scale. Many scientists, both in academia and in industry, have turned to microwave synthesis as a frontline methodology for their projects. This review highlights applications of microwave chemistry in organic synthesis, for drug discovery, development and discusses some of the underlying phenomena involved.

KEY WORDS: *Microwaves, Organic synthesis, Dielectric heating, Applications.*

INTRODUCTION

In the background of green chemistry, microwave irradiation provides an alternative to the conventional methods, for heating or introducing energy into the system. It utilizes the ability of mobile electric charges present in liquid or conducting ions in solid to transform electromagnetic energy into heat. Microwave-assisted reactions are fast, clean, economic and eco-friendly¹ and this technique has been proposed as the “technology of tomorrow”.

Chronology

Microwave heating began to gain wide acceptance following papers in 1986 by the groups of Gedye and Giguere / Majetich, although the use of microwave heating in chemical modification can be traced back to the 1950s^{2,3}. In the early days of microwave synthesis, experiments were typically carried out in sealed teflon or glass vessels in a domestic household microwave oven without any temperature or pressure measurements¹. Kitchen microwave ovens are not designed for laboratory usage: acids and solvents corrode the interiors quickly and there are no safety controls. The results were often violent explosions due to the rapid uncontrolled heating of organic solvents under closed vessel conditions. In the 1990s several groups started to experiment with solvent-

free microwave chemistry, which eliminated the risk of explosions. Here, the reagents were pre-adsorbed onto either a more or less microwave transparent inorganic support (i.e. silica, alumina or clay) or a strongly absorbing one (i.e. graphite)⁴ that additionally may have been doped with a catalyst or reagent. Particularly in the beginning of Microwave assisted organic synthesis, the solvent-free approach was very popular since it allowed the safe use of domestic microwave ovens and standard open vessel technology. A large number of interesting transformations using dry-media reactions have been published in the literature^{5,6}, yet technical difficulties relating to non-uniform heating, mixing, and the precise determination of the reaction temperature remained unsolved, when scale-up issues needed to be addressed. Alternatively, MAOS was often carried out using standard organic solvents under open vessel conditions. If solvents are heated by microwave irradiation at atmospheric pressure in an open vessel, the boiling point of the solvent typically limits the reaction temperature that can be achieved. In order to achieve high reaction rates, high-boiling microwave absorbing solvents were frequently used in open-vessel microwave synthesis^{7,8}. However, the use of these solvents presented serious challenges during product isolation and recycling of solvent. In addition, the risks associated with the flammability of organic solvents in a microwave field and the lack of available dedicated microwave reactors allowing adequate temperature and pressure control were major concerns.

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MICROWAVES

Microwave chemistry involves the use of microwave radiations to conduct chemical reactions, and essentially pertains to chemical analysis and chemical synthesis. Microwaves lie in the electromagnetic spectrum between infrared waves and radio waves. They have wavelengths between 0.01 and 1 meter, and operate in a frequency range between 0.3 and 30 GHz (Fig. 1).

However, for their use in laboratory reactions, a frequency of 2.45 GHz is preferred, since this frequency has the right penetration depth for laboratory reaction conditions. Beyond 30 GHz, the microwave frequency range overlaps with the radio frequency range. The microwave electromagnetic spectrum is divided into sub-bands comprising the following frequency ranges (Table 1).

The lower microwave frequency ranges (L band) are used for the purpose of communication, however, the higher frequency ranges (W band) are reserved for analytical techniques such as spectroscopy^{1,11}.

Microwave Heating

The mechanism of microwave heating involves agitation of

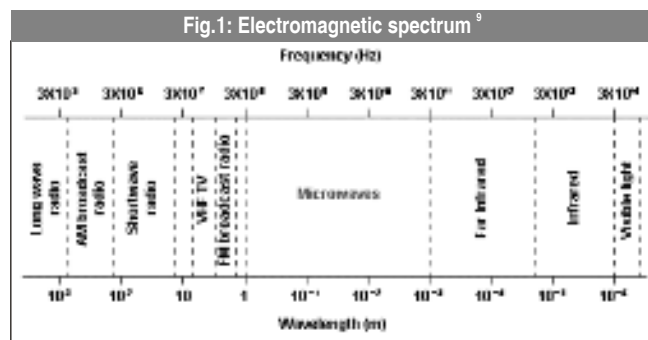


Table 1: Microwave frequency bands¹⁰

Bands	Frequency
L	1-2 GHz
S	2-4 GHz
C	4-8 GHz
X	8-12 GHz
Ku	12-18 GHz
K	18-26 GHz
Ka	26-40 GHz
Q	30-50 GHz
U	40-60 GHz
V	46-56 GHz
W	56-100 GHz

polar molecules or ions that oscillate under the effect of an oscillating electric or magnetic field. In the presence of an oscillating field, particles try to orient themselves with the field. However, resisting forces like inter-particle interaction and electric resistance restricts the motion of particles thus results into random motions which in turn generate heat. All the materials are not amenable to microwave heating as response of various materials to microwave radiation is diverse. Based on their response to microwaves, materials can be broadly classified as follows:

- Materials that are transparent to microwaves, e.g. sulphur
- Materials that reflect microwaves, e.g. copper
- Materials that absorb microwaves, e.g. water

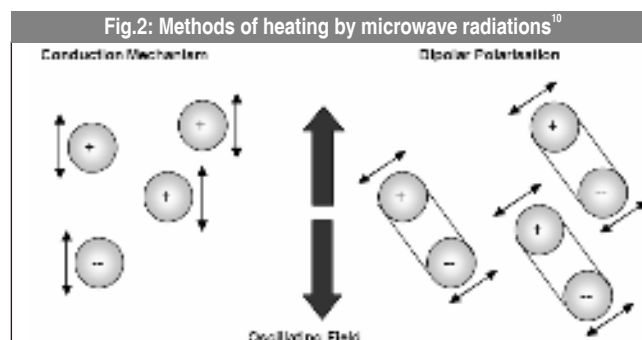
Microwave absorbing materials are of utmost important for microwave chemistry and three main different mechanisms are involved for their heating (Fig. 2) namely¹²:

Dipolar polarization

Polar molecules are the ideal material for dipolar polarization method. On exposure to an oscillating electromagnetic field of appropriate frequency, polar molecules try to follow the field and align themselves in phase with the field. However, owing to inter-molecular forces, polar molecules experience inertia and are unable to follow the field. This results in the random motion of particles, which in turn generates heat. Dipolar polarization can generate heat by either one or both the following mechanisms:

- Interaction between polar solvent molecules such as water, methanol and ethanol.
- Interaction between polar solute molecules such as ammonia and formic acid.

The key requirement for dipolar polarization is that the frequency range of the oscillating field should be appropriate to enable adequate inter-particle interaction. If the frequency range is very high, inter-molecular forces will stop the motion of a polar molecule before it tries to follow the field, resulting in inadequate inter-particle interaction. On the other hand, if the frequency range is low, the polar molecule gets sufficient



time to align itself in phase with the field. Hence, no random interaction takes place between the adjoining particles. Microwave radiation has the appropriate frequency (0.3-30 GHz) to oscillate polar particles and enable enough inter-particle interaction. This makes it an ideal choice for heating polar solutions. In addition, the energy in a microwave photon (0.037 kcal/mol) is very low, relative to the typical energy required to break a molecular bond (80-120 kcal/mol). Therefore, microwave excitation of molecules does not affect the structure of an organic molecule and the interaction is purely kinetic.

Conduction mechanism

The conduction mechanism generates heat through resistance to an electric current. The oscillating electromagnetic field generates an oscillation of electrons or ions in a conductor, resulting in an electric current. This current faces internal resistance, which heats the conductor. Major limitation of the method is that it is not applicable for materials with high conductivity, since such materials reflect most of the energy that falls on them.

Interfacial polarization

The interfacial polarization method can be considered as a combination of the conduction and dipolar polarization mechanisms. It is important for heating systems that comprise a conducting material dispersed in a non-conducting material. For example, consider the dispersion of metal particles in sulphur. Sulphur does not respond to microwaves and metals

reflect most of the microwave energy they are exposed to, but combining the two makes them a good microwave-absorbing material. However, for this to take place, metals have to be used in powder form. This is because, unlike a metal surface, metal powder is a good absorber of microwave radiation. It absorbs radiation and is heated by a mechanism that is similar to dipolar polarization. The environment of the metal powder acts as a solvent for polar molecules and restricts the motion of ions by forces that are equivalent to inter-particle interactions in polar solvents. These restricting forces under the effect of an oscillating field induce a phase lag in the motion of ions, resulting in random motion of ions and ultimately heating of the system¹³⁻¹⁷.

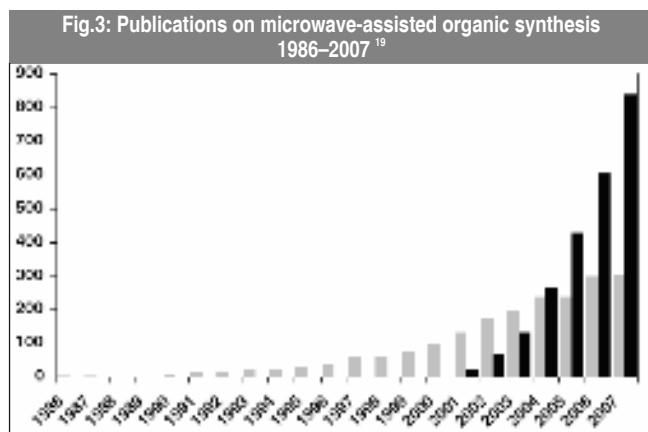
Evolution of Microwave Chemistry

Microwave technology originated in 1946, when Dr. Percy Le Baron Spencer, while conducting laboratory tests for a new vacuum tube called a magnetron (device that generates an electromagnetic field), accidentally discovered that a candy bar in his pocket melted on exposure to microwave radiation. Dr. Spencer developed the idea further and established that microwaves could be used as a method of heating. Subsequently, he designed the first microwave oven for domestic use in 1947¹⁸. Since then, the development of microwave radiation as a source of heating has been very gradual (Table 2).

This is evident from surveying the recently published literature in the area of MAOS (Fig. 3).

Table 2: Evolution of microwave chemistry¹⁰

1946	Microwave radiation was discovered as a method of heating
1947	First commercial domestic microwave oven was introduced
1978	First microwave laboratory instrument was developed by CEM Corporation to analyse moisture in solids
1980-82	Microwave radiation was developed to dry organic materials
1983-85	Microwave radiation was used for chemical analysis.
1986	Robert Gedye, Laurentian University, Canada; George Majetich, University of Georgia, USA; and Raymond Giguere of Mercer University, USA, published papers relating to microwave radiation in chemical synthesis
1990s	Microwave chemistry emerged and developed as a field of study for its applications in chemical reactions
1990	Milestone s.r.l. generated the first high pressure vessel (HPV 80) for performing complete digestion of materials like oxides, oils and pharmaceutical compounds
1992- 96	CEM developed a batch system reactor, and a single mode cavity system that was used for chemical synthesis
1997	Milestone s.r.l and Prof. H.M (Skip) Kingston of Duquesne University culminated a reference book titled “ Microwave-Enhanced Chemistry – Fundamentals, Sample Preparation, and Applications ”, and edited by H. M. Kingston and S. J. Haswell
2000	First commercial microwave synthesizer was introduced to conduct chemical synthesis



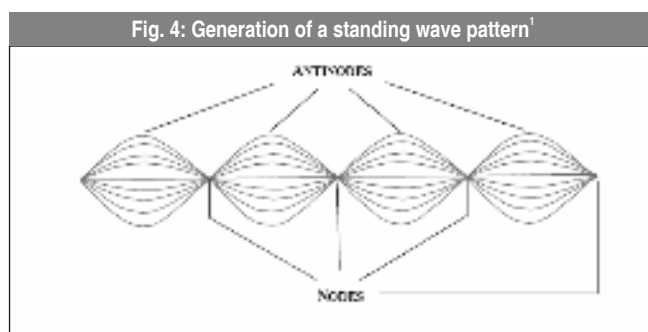
Gray bars: Number of articles involving MAOS for selected synthetic organic chemistry journals (J. Org. Chem., Org. Lett., Tetrahedron, Tetrahedron Lett., Synth. Commun, Synthesis, Synlett.). **Black bars:** Number of publications 2001–2007 reporting MAOS experiments.

Microwave Chemistry Apparatus

The following are the two categories into which microwave chemistry apparatus are classified:

Single-mode apparatus

The differentiating feature of a single-mode apparatus is its ability to create a standing wave pattern, which is generated by the interference of fields that have the same amplitude but different oscillating directions. This interface generates an array of nodes where microwave energy intensity is zero, and



an array of antinodes where the magnitude of microwave energy is at its highest (Fig. 4).

The factor that governs the design of a single-mode apparatus is the distance of the sample from the magnetron. This distance should be appropriate to ensure that the sample is placed at the antinodes of the standing electromagnetic wave pattern (Fig. 5).

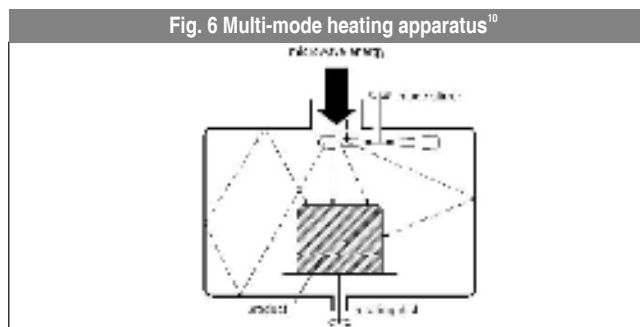
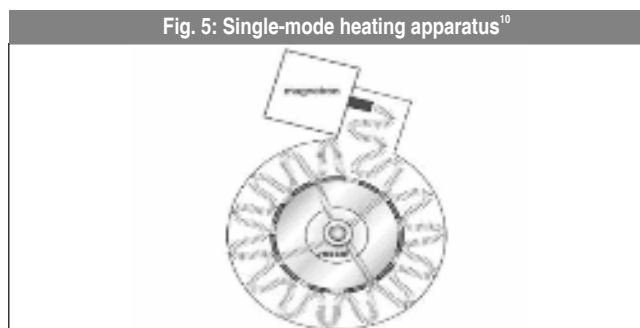
One of the limitations of single-mode apparatus is that only one vessel can be irradiated at a time. However, after the completion of the reaction period, the reaction mixture can

be rapidly cooled by using compressed air. As a result, the apparatus becomes more user-friendly. These apparatus can process volumes ranging from 0.2 to about 50 mL under sealed-vessel conditions (250 °C, ca. 20 bar) and volumes around 150 mL under open-vessel reflux conditions. Single-mode microwave heating equipment is currently used for small-scale drug discovery, automation and combinatorial chemical applications. An advantage of single-mode apparatus is their high rate of heating.

Multi-mode apparatus

An essential feature of a multi-mode apparatus is the deliberate avoidance of generating a standing wave pattern inside it (Fig. 6).

The goal is to generate as much chaos as possible inside the apparatus. The greater the chaos, the higher is the dispersion of radiation, which increases the area that can cause effective heating inside the apparatus. As a result, a multi-mode microwave heating apparatus can accommodate a number of samples simultaneously for heating, unlike single-mode apparatus where only one sample can be irradiated at a time. Owing to this characteristic, a multi-mode heating apparatus is used for bulk heating and carrying out chemical analysis processes such as ashing, extraction, etc. In large multi-mode apparatus, several liters of reaction mixture can be processed in both open and closed-vessel conditions. Recent research has resulted in the development of continuous-flow reactors for single- and multi-mode cavities that enabled preparation of materials in kilograms. A major limitation of multi-mode apparatus is that, heating samples cannot be controlled efficiently because of lack of temperature uniformity. This is



largely due to the chaos generated, which makes it difficult to create equal heating conditions for samples that are heated simultaneously²⁰⁻²⁸.

Benefits of Microwave Chemistry

Microwave radiation has proved to be a highly effective heating source in chemical reactions. Microwaves can accelerate the reaction rate, provide better yields and uniform and selective heating, achieve greater reproducibility of reactions and help in developing cleaner synthetic routes.

Increased rate of reactions and percentage yield

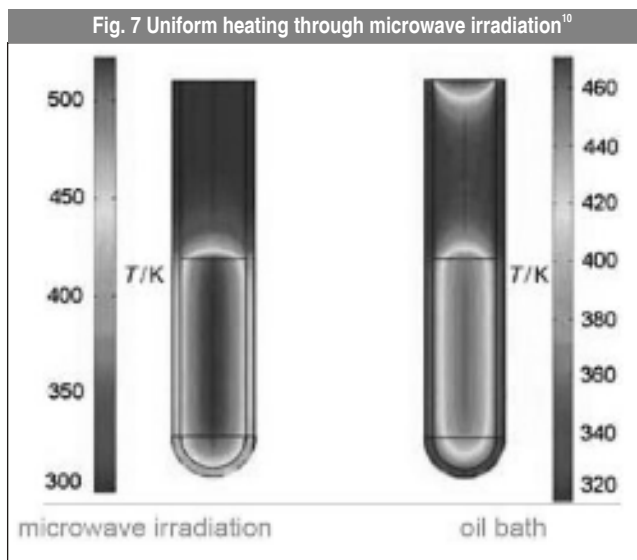
Compared to conventional heating, microwave heating enhances the rate of certain chemical reactions by 10 to 1,000 times. This is due to its ability to increase the temperature of a reaction, for instance, synthesis of fluorescein, which usually takes about 10 hours by conventional heating methods, can be conducted in only 35 minutes by means of microwave heating (Table 3).

In certain chemical reactions, microwave radiations produces higher yields compared to conventional heating methods, for example, microwave synthesis of aspirin results in an increase in the yield of the reaction, from 85% to 92% (Table 3).

Efficient and uniform heating

Heating by microwave radiations is highly efficient and energy saving process. This is because microwaves heat up just the sample and not the apparatus, and therefore energy consumption is less. A typical example is the use of microwave radiation in the ashing process. Microwave ashing systems can reach temperatures of over 800 °C in 50 minutes, they eliminate the lengthy heating-up periods associated with conventional electrical resistance furnaces thus significantly lowers average energy costs.

Microwave radiation, unlike conventional heating methods, provides uniform heating throughout a reaction mixture (Fig. 7), raises the temperature of the whole volume simultaneously (bulk heating), whereas in the oil-heated tube, the walls of the oil bath get heated first followed by the reaction mixture in immediate contact with the vessel wall



and ultimately the bulk. As a result of this distributed heating in an oil bath, there is always a temperature difference between the walls and the solvent. Microwave heating involves excitement of only the solvent and the solute particles, resulting in uniform heating of the solvent. This feature allows the chemist to place reaction vessels at any location in the cavity of a microwave oven. It also proves vital in processing multiple reactions simultaneously, or in scaling up reactions that require identical heating conditions²⁹

Selective heating

Selective heating is based on the principle that different materials respond differently to microwaves. Some materials are transparent whereas others absorb microwaves. Therefore, microwaves can be used to heat a combination of such materials, for example, the production of metal sulphide with conventional heating requires weeks because of the volatility of sulphur vapours. Rapid heating of sulphur in a closed tube results in the generation of sulphur fumes, which can cause an explosion. However, in microwave heating, since sulphur is transparent to microwaves, only the metal gets heated. Therefore, reaction can be carried out at a much faster rate, with rapid heating, without the threat of explosion^{4,5,30}.

Table 3: Comparative study¹⁰

Reaction	Duration (in min.)		% yield	
	Conventional	Microwave	Conventional	Microwave
Synthesis of fluorescein	600	35	70	82
Condensation of benzoin with urea	60	8	70	73
Biginelli reaction	360	35	70	75
Synthesis of aspirin	130	1	85	92

Eco-friendly

Reactions conducted by microwaves are cleaner and more environmentally friendly than conventional heating methods. Microwaves heat the compounds directly, therefore, usage of solvents in the chemical reaction can be reduced or eliminated, for example, Hamelin developed an approach to carry out a solvent-free chemical reaction on a sponge-like material with the help of microwave heating. The reaction is conducted by heating a spongy material such as alumina. The chemical reactants are adsorbed to alumina and on exposure to microwaves, react at a faster rate than conventional heating. The use of microwaves has also reduced the amount of purification required for the end products of chemical reactions involving toxic reagents^{4,5,30}.

Reproducibility

Reactions with microwave heating are more reproducible compared to conventional heating because of uniform heating and better control of process parameters. The temperature of chemical reactions can also be easily monitored. This is of particular relevance in the lead optimization phase of the drug development process in pharmaceutical companies^{4,5,30}.

Applications of Microwave Chemistry

Microwave chemistry is applicable in various industries such as the biotechnology, pharmaceuticals, petroleum, plastics, chemicals etc and major applications have been developed in the field of analytical chemistry and chemical synthesis. Due to the successful development of commercial instrumentation, microwave dielectric heating is now being increasingly applied in chemical reactions. However, most of these applications have been limited to small-scale use in laboratories and have not been extended to the production level.

The major industrial applications of microwave chemistry can be segmented as:

1. Applications in Analytical Chemistry

The various applications of microwave radiation in analytical chemistry are:

1.1. Ashing

Ashing is used in various analytical laboratories to determine the ash content in a sample, for the purpose of process and quality control. Microwave heating is extensively used for ashing in the petroleum and fuels, plastics, pharmaceuticals and food industries. In most of these industries, microwave-powered muffle furnaces, which are specifically meant for laboratory use, are used for ashing. These microwave muffle furnaces have proven to be more efficient (about 97%) compared to conventional muffle furnaces. They can reach

high temperatures ranging between 1,000 °C and 1,200 °C and can also process a large number of samples simultaneously³¹.

1.2. Digestion

Digestion is the process by which samples are broken down to their basic constituents for chemical analysis. Microwave digestion systems are used in analytical laboratories for sample decomposition and preparation. It involves the heating of microwave-absorbing reagents inside a pressurized, microwave-transparent container, in contrast to conventional open vessel digestion. Pressurization allows higher temperatures to be achieved in short period and it increases the speed of digestion. Rapid heating accelerates the reaction rate exponentially and results in an approximately 100-fold decrease in the time required for the process of digestion at 175 °C, compared to such a process conducted at 95 °C. Microwave radiation has now become the technology of choice for sample preparation trace and ultra-trace metals analysis and is being used in the digestion of even the toughest organic or inorganic samples in diverse industries³².

1.3 Extraction

Microwave extraction has proved to be more effective and efficient than its conventional counterpart, the Soxhlet extraction method. The Soxhlet extraction, which is a standard technique, is a continuous solvent extraction method. Extraction systems are used to conduct routine solvent extractions of soils, sediments, sludge, polymers and plastics, pulp and paper, biological tissues, textiles and food samples. Experiments have proved that microwaves, in comparison with the Soxhlet extraction, use a lesser volume of solvent and sample and perform extraction at a much faster rate. For example, it has been observed that about 500 microwave extractions can be performed for a given solvent, compared to just 32 Soxhlet extractions³².

1.4 Moisture analysis

Application of microwave assisted moisture analysis has been extended to food and beverage, chemical, environmental, organic and pharmaceutical industries and has been found to be highly effective in reducing testing time. Microwave moisture analysis is specifically applied at product development stages such as process and quality control, testing of raw materials, intermediate and finished products³².

2. Applications in Chemical Synthesis

Application of microwave radiation in chemical synthesis encompasses its use in the acceleration of chemical synthesis. Microwave-enhanced synthesis allows organic chemists to work faster, generate higher yields, and increase product

purity. In addition, due to the availability of high-capacity microwave apparatus, the yields of the experiments have now easily scaled up from milligrams to kilograms, without the need to alter reaction parameters. Microwave organic synthesis is the main component of microwave-assisted chemical synthesis.

2.1 Organic synthesis

Organic synthesis is the preparation of a desired organic compound from available starting materials. Microwave-assisted organic synthesis has been the one of the most researched applications of microwaves in chemical reactions. Chemists have successfully conducted a large range of organic reactions. These include³³:

1. Diels-Alder reaction
2. Heck reaction
3. Suzuki reaction
4. Mannich reaction
5. Hydrogenation of [beta]-lactams
6. Hydrolysis
7. Dehydration
8. Esterification
9. Cycloaddition reaction
10. Epoxidation
11. Reductions
12. Condensations
13. Protection and deprotection
14. Cyclisation reactions.

Microwave-assisted organic synthesis is being widely applied in the pharmaceuticals industry, particularly for developing compounds in the lead optimization phase of drug development. In this phase, chemists use diverse synthetic techniques to develop candidate drugs from lead compounds. Based on reaction conditions, organic synthesis reactions can be conducted in the following ways:

2.1.1. Organic synthesis at atmospheric pressure

Microwave-assisted organic reactions can be conveniently conducted at atmospheric pressure in reflux conditions e.g. Diels-Alder reaction of maleic anhydride with anthracene. In the presence of diglyme (boiling point 162 °C), this reaction can be completed in a minute, with a 90% yield. However, the conventional synthetic route, which uses benzene, requires 90 minutes. High boiling solvents are preferred in microwave-assisted organic synthetic reactions.

2.1.2 Organic synthesis at elevated pressure

Microwaves can be used to directly heat the solvent in sealed microwave-transparent containers. The sealed container helps in increasing the pressure in the reactor, which facilitates the reaction that will take place at much higher temperatures. This results in a substantial increase in the reaction rate of microwave-assisted organic. However, increase in the reaction rate of any chemical synthesis depends on three factors: volume of the vessel, the solvent to space ratio, and the solvent boiling point³⁴.

2.1.3. Organic synthesis in dry media

Microwaves have been applied to organic synthesis in dry media, using solid supports (i.e. alumina, montmorillonite clay, alkali metal fluoride doped alumina and silica.) Microwave radiation, based on solid supports, has been highly successful in reducing the reaction time for condensation, acetylation and deacetylation reactions, for example, deacetylation of a protected compound such as alcoholic acetate held on a support material. The microwave-assisted reaction could be completed within two to three minutes, compared to conventional oil-bath heating at 75 °C for 40 hours³³.

2.2 Inorganic synthesis

2.2.1. Synthesis of organometallic and coordination compounds

Microwave radiation has been successful in accelerating the reaction rate for the generation of organometallic and coordination compounds, which are produced by generating covalent bonds between organic compounds and metals.

2.2.2. Synthesis of intercalation compounds

Applications of microwave chemistry for intercalation compounds have been tested recently. Intercalation compounds comprise organic or organometallic compounds that are incorporated between layers of oxides and sulphides. Conventional heating methods for the preparation of intercalation compounds, such as the intercalation of pyridine or its derivatives are slow and have limitations w.r.t. the yield obtained.

2.2.3. Synthesis of ceramic products

Microwave processing of ceramic materials has reached a high degree of maturity. In ceramic production industry, the removal of solvent or moisture is a critical step in the generation of ceramic products. Initially, the use of microwaves was limited to the effective removal of solvents from solid samples. It is estimated that for materials with a water content below 5%, microwave drying is efficient than conventional drying methods. However, over the past few

years, the utility of microwaves has increased due to other advantages. It has been proven that microwave heating provides better uniform heating than conventional heating methods. Ceramics are widely used in electrical components, sanitary-ware industries, and in many other industries.

3. Applications in Polymer Chemistry

Polymer chemistry, including ceramic processing, forms the single-largest application area of microwave chemistry. The use of polar reactants in polymerization reaction results in controlled synthesis and a combination of this with direct heating of reactants makes microwave heating an economically viable option. Curing is a polymerization process, which transforms a liquid resin to a solid, creating the maximum physical properties attainable from the materials. Using microwave radiation in curing has greatly increased the rate of the reactions. It has been found that the rate of a curing reaction, using microwaves, is not dependent on the power applied but on the way the pulse is applied^{35,36}.

CONCLUDING REMARKS

There is no doubt that microwaves can be used to great effect in organic synthesis; the “in situ” generation of heat is very efficient and can be used to significantly reduce reaction times of numerous synthetically useful organic transformations. Thus microwave assisted organic synthesis has advantages over conventional technology: it is more energy efficient and it can lead to improved isolated yields of products. The advantages of this enabling technology have also been exploited in the context of multistep total synthesis and medicinal chemistry/drug discovery and have additionally penetrated related fields such as polymer synthesis, nanotechnology and biochemical processes. The obvious application of this approach to combinatorial synthesis should provide a major impetus for further developments in this area; a particularly important feature will be the continued development of microwave assisted solid phase reactions. The effects of microwave radiation on chemo-, regio- and stereoselectivity in synthesis and the continued quest for evidence of a non-thermal microwave effect are also important aspects which need to be addressed. It is clear that microwave assisted synthesis, whilst still at an early stage of development, has much to offer synthetic chemists. It is likely that, with increased activity in this exciting area, widespread acceptance of this technology will result in the microwave oven becoming an integral part of every modern organic synthesis laboratory.

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